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Total Synthesis of the Polyoxygenated Sesquiterpenes Guignarderemophilanes C and D

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Dedication ((optional))

The total syntheses of the neural anti-inflammatory agents guignarderemophilanes C and D have been accomplished for the first time starting from γ-hydroxy carvone in 15 and 14 steps, respectively. The presented synthetic route proceeds *via* a known intermediate, whose synthesis has been elaborated in our group in the course of the total synthesis of the sesquiterpenoid periconianone A. Key for the successful conversion of this intermediate into both targets was finding a suitable strategy to install the 1,2,3-trihydroxylated A-ring scaffold. For this purpose, we effectively employed a Mitsunobu inversion, epoxidation, and regioselective epoxide opening sequence, before the bicyclic ring system was constructed by an aldol condensation reaction on a sterically demanding substrate. Our reported synthesis set the stage for SAR studies to prepare even more potent compounds by modification and derivatization of the natural product's scaffold.

Keywords: Total Synthesis • Natural Products • Terpenoids • Neural Anti-Inflammatory • Sesquiterpenes

Introduction

Eremophilane sesquiterpenes present a group of natural products built up on a 15-carbon skeleton characterized by a decalin core unit connected to two one-carbon substituents at C4 and C5, and an isopropenyl or isopropyl group at C7 (Figure 1, **A**). The first member of this family had been isolated and reported by J. L. Simonsen and coworkers in 1932, and named eremophilone.[1] Since this discovery, many new compounds bearing this structural motif have been described, featuring a number of biological activities such as anti-inflammatory, anti-tumor or anti-bacterial.[2–4] Structural diversity for eremophilane sesquiterpenes, as for terpenes in general, is generated by a variety of oxidation events taking place during biosynthesis. All of the 15 carbons are known to be accessible for oxidation, with hydroxylation often taking place at C1, C3, C7 and/or C12. However, C1,C2,C3-trihydroxylated eremophilanes are rare: besides the two target compounds, only four such natural products have been described to date, *viz*. ligumacrophyllatin,[5] sporogen AO-2[6], 1β,8β-dihydroxy-2β,3α-diangeloyloxyeremophil-7(11)-en-8α(12)-olide,[7] and guignarderemophilane F.[8] The former is characterized by an all α–configuration of the three hydroxy groups (1α,2α,3α); the second by a 1α,2β,3α-configuration; the third by a 1β,2β,3α-configuration; and the latter as a stereoisomer of guignarderemophilane C by a 1β,2α,3α-configuration. Neither of these compounds have been synthesized yet and there is no reported preparative strategy addressing this unusual trihydroxylated A-ring motif. Recently, two natural products with a 1α,2β,3β-trihydroxylated scaffold have been isolated for the first time from the fungus *Guignardia mangiferae*, and named guignard-eremophilanes C (**1**) and D (**2**).[9] The fungus *Guignardia mangiferae* is an endosymbiont of plants such as *Gelsemium elegans*, whose extracts are used in traditional Chinese medicine as nervous relaxant and for the treatment of pain.[10] Both eremophilanes showed neural anti-inflammatory activity by inhibiting the LPS-induced NO production in BV2 cells with IC_{50} values of 6.4 and 4.2 μM, respectively.[9] Therefore, guignarderemophilanes C and D may potentially serve as lead compounds for developing treatment options for neuro-degenerative diseases.

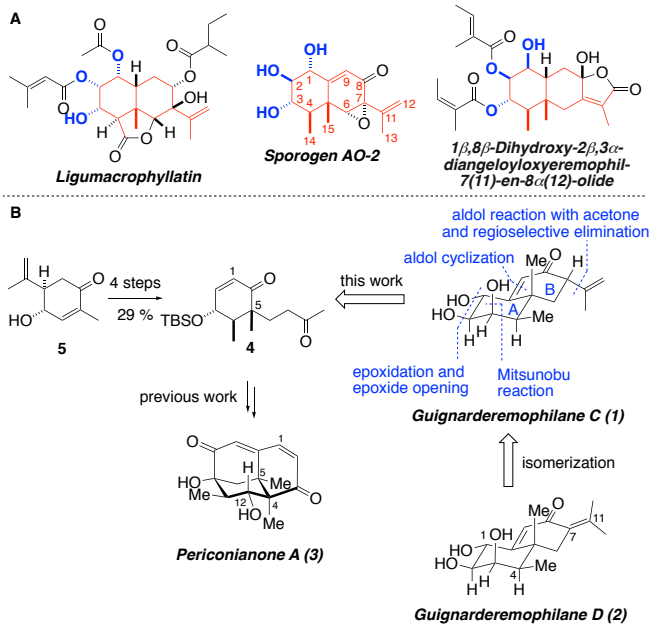


Figure 1. A: Eremophilane sesquiterpenes containing a 1,2,3-trihydroxylated A-ring. **B**: Retrosynthetic analysis of guignarderemophilanes C (**1**) and D (**2**).

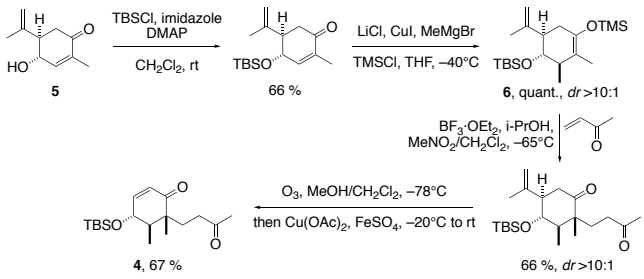
Besides the unusual 1,2,3-trihydroxylated scaffold, another striking structural feature of both eremophilane sesquiterpenoids is the presence of five contiguous stereogenic centers in the six-membered A-ring, one of which is quaternary. Guignarderemophilane C contains an additional stereogenic center (C7) connected to an isopropenyl moiety with unsaturation in β,γ position of the carbonyl group, which is prone to isomerize to the α,β-unsaturated ketone, as in

guignarderemophilane D. From a retrosynthetic perspective, we envisioned to use cyclohexanone derivative **4**, whose synthesis has been elaborated in our group in the course of the total synthesis of the tricyclic sesquiterpenoid periconianone A (**3**).[11] As a first challenge, we addressed the stereoselective installation of the aforementioned three hydroxy groups. To this end, we envisioned inversion of the stereocenter at C3 by Mitsunobu reaction of cyclohexanone **4**, as well as a diastereoselective epoxidation and regioselective epoxide opening sequence to install the C1 and C2 hydroxy groups. Functionalization at C7 to install the three-carbon unit for completion of the 15-carbon skeleton was envisioned by an aldol addition of acetone, followed by regioselective dehydration.

In this study, we present the first total syntheses of guignarderemophilane C and D starting from γ-hydroxy carvone (**5**) in 15 and 14 steps, respectively. Additionally, in the course of our synthetic endeavor, we observed a spontaneous aldol condensation under specific epoxidation reaction conditions. The main challenge consisted in finding a suitable sequence for the introduction of the functional groups on the carbon skeleton with respect to the substitution pattern in the A-ring. Key for the successful synthesis was to establish all stereogenic centers in the A-ring before the B-ring was constructed by aldol cyclization.

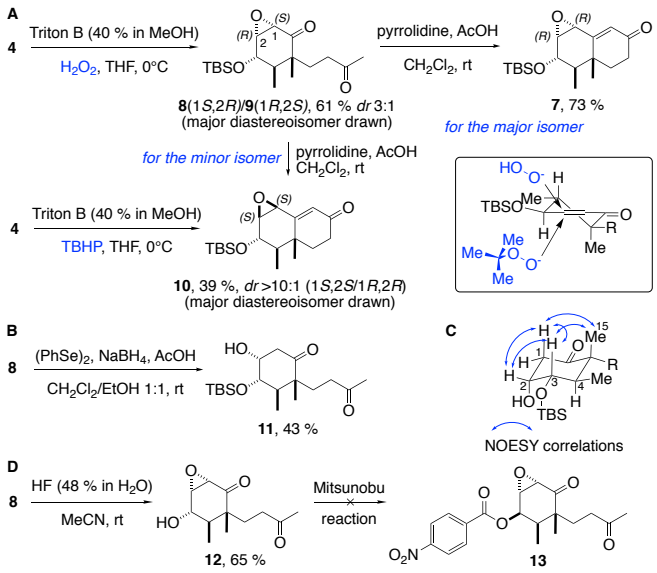
Results and Discussion

The synthesis commenced from known enone **4** (Scheme 1),[11] which was prepared from γ-hydroxy carvone (**5**) in 29 % yield over four steps: TBS protection of the secondary alcohol was followed by a 1,4-addition of methyl cuprate to the enone, and the formed enol ether was trapped with TMSCl to form the silyl enol ether **6**. Lewis acid-mediated Michael addition on methyl vinyl ketone to install the alkyl group at C5 was performed with high diastereoselectivity (*dr* > 10:1). A Criegee fragmentation then removed the isopropenyl moiety, used as directing group for the stereoselective installation of the substituents at C3, C4 and C5, to give enone **4**.



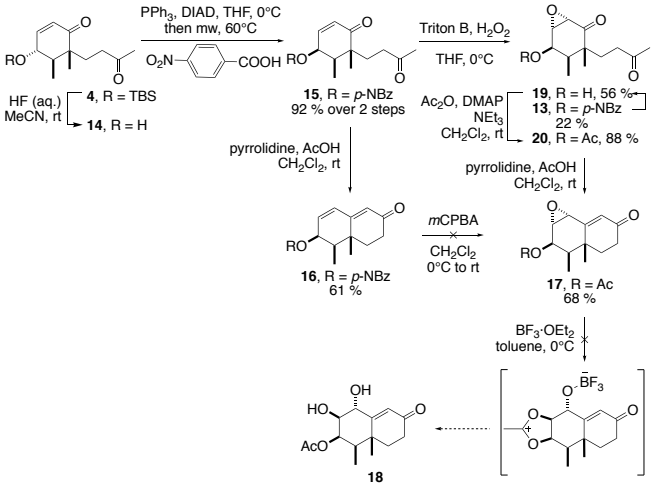
Scheme 1. Synthesis of the previously reported precursor **4.**

We had at first envisioned the synthesis to proceed by epoxidation of the C1=C2 double bond of enone **4**, followed by an aldol condensation to form the octalone core **7** (Scheme 2). While screening conditions for the epoxidation, we found diverging diastereoselectivities for different peroxide sources: with hydrogen peroxide,[12][13] epoxidation on the same face as the OTBS group in the A-ring was observed and we isolated epoxy ketones **8** and **9** with a *dr* of 3:1. Using *tert*-butyl hydrogen peroxide, the epoxidation exclusively took place (*dr* > 10:1) on the opposite face with respect to the OTBS group. Observations for similar substrates with comparable stereochemical outcome have already been described in the literature.[14][15] Although the obtained selectivities cannot be fully explained based on steric or stereoelectronic effects or both, it might be reasonable to argue that the attack for the sterically more demanding *tert*-butyl hydrogen peroxide preferably takes place from the less shielded face of the six-membered ring at C2 of **4** with the OTBS group in a pseudoequatorial position. However, applying the described conditions for the latter reaction, instead of the epoxy ketone, we observed spontaneous closure of the B-ring to form the octalone **10** (Scheme 2, **A**). To the best of our knowledge, this is the first reported example of a tandem epoxidation–aldol condensation sequence. After work-up of the reaction mixture, the ^{1}H NMR spectrum of the crude product indicated formation of octalone **10** and an unknown compound in a ratio of 4:1. When the reaction time was decreased from five hours to one hour, the ratio of the two products increased to 2:3 in favor of the unknown compound. This byproduct was identified to be the bicyclic γ,δ-epoxy β-hydroxy ketone by isolation and structure elucidation based on 2D NMR spectra. Therefore, we hypothesize epoxidation taking place prior to aldol addition to form the isolated intermediate, which can subsequently undergo dehydration to form octalone **10**. An aldol addition, epoxidation and dehydration pathway is less likely, since the electron rich C1=C2 double bond of the hypothetically formed bicyclic aldol addition product would not undergo epoxidation under the given reaction conditions. Additionally, the intermediacy of γ,δ-epoxy β-hydroxy ketone rules out a pathway in which nucleophilic epoxidation takes place after aldol condensation in a 1,6-fashion to the dienone system. Cyclization of epoxy ketone **8** (major diastereoisomer) provided access to the other octalone diastereoisomer **7**.[16] The absolute configuration of both epoxy ketones **8** and **9** as well as octalones **7** and **10** could not be established by NOESY NMR spectroscopy. Therefore, we performed reductive cleavage of epoxy ketone **8** to give β-hydroxy ketone **11** using the reactive species Na[PhSeB(OEt)$_3$] prepared *in situ* from (SePh)$_2$, NaBH$_4$ and AcOH in CH_2Cl_2/EtOH (Scheme 2, **B**).[17][18] NOESY NMR spectroscopy showed correlations of H1$_{ax}$ to H2, H3 and H15; of H2 to both H1$_{ax}$ and H1$_{eq}$; of H3 to H1$_{ax}$, H2, H14 and H15 (Scheme 2, **C**). Coupling constants for the proton signals at positions C1, C2, C3 and C4 ($^3J_{H1ax\text{-}H2eq}$ = 3.5 Hz; $^3J_{H1eq\text{-}H2eq}$ = 3.7 Hz; $^3J_{H2eq\text{-}H3ax}$ = 2.7 Hz; $^3J_{H3ax\text{-}H4ax}$ = 10.0 Hz) further corroborated the assignment of the absolute configuration at stereogenic center C2 of **11,** and hence provided substantial evidence for the configurational assignment of intermediates **7**, **8**, **9** and **10** obtained after epoxidation.



Scheme 2. A: Epoxidation of enone **4** and tandem epoxidation/aldol condensation approach; **B**: Reductive cleavage of epoxy ketone **8** to β-hydroxy ketone **11**; **C**: Key NOESY correlations for the configurational assignment of the C2 hydroxy group in **11**; **D**: Investigation of the Mitsunobu reaction of epoxy ketone **12**.

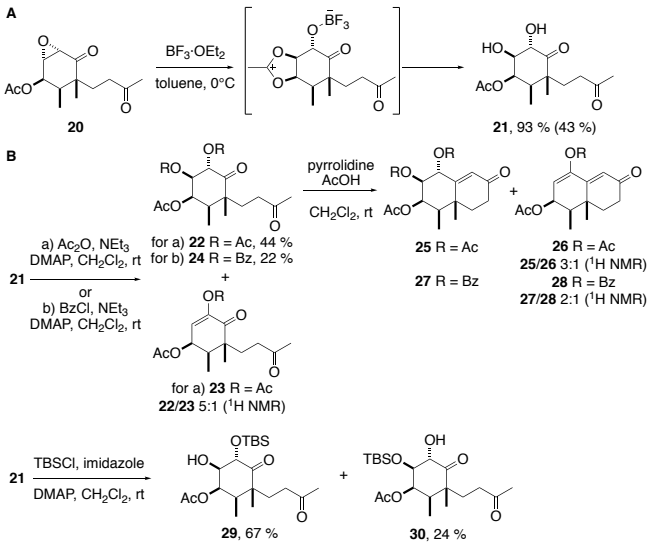
However, epoxy alcohol **12** was found completely unreactive towards Mitsunobu reaction conditions (up to 150°C under microwave irradiation)[19][20] and did not form the ester **13** after the TBS-protecting group in **8** had been removed (Scheme 2, **D**). Therefore, we decided to use a route which addresses the inversion of the configuration at C3 first. TBS deprotection of enone **4** with aqueous HF in MeCN already set the stage for the Mitsunobu reaction. No conversion was monitored applying standard Mitsunobu protocols using PPh_3, DIAD and acetic acid as nucleophile.[19][20] It is well documented in literature that acetic acid can react sluggishly in the Mitsunobu reaction.[21] Therefore, we decided to investigate the reaction using the more suitable nucleophile *para*-nitrobenzoic acid. Key for the successful transformation was to use Volante's method,[22] a modified Mitsunobu procedure, which involves mixing of PPh_3 and DIAD first before adding the alcohol **14** and the acid to the reaction mixture at 0°C. After the mixture was warmed up to room temperature and stirred for 35 min, heating in the microwave at 60°C for one hour led to formation of the ester **15** with full inversion at C3 and 92 % yield over two steps (Scheme 3). Conditions used earlier for the tandem epoxidation and aldol reaction of enone **4** did not result in the transformation of enone **15** to its desired epoxy octalone. Fortunately, aldol cyclization of the ester **15** *via* an intermediate enamine upon reaction with pyrrolidine in the presence of AcOH furnished the doubly unsaturated octalone **16** in 61 % yield. There are only few literature reports on the epoxidation of γ,δ-unsaturated octalones, and unfortunately, the C1=C2 double bond could not be epoxidized by *m*CPBA.[23] However, we succeeded to form the epoxide of monocyclic **15**. Epoxidation of electron-poor double bonds is usually conducted under basic conditions using a nucleophilic peroxide reagent. With the base-sensitive ester moiety at C3, a functional group necessary in the envisioned regioselective epoxide opening (**17** → **18**), we tried to find conditions avoiding hydrolysis of this ester. We were able to optimize the yield of the epoxidation reaction up to 82 % in favor of epoxy ketone **13** with an intact ester group on a small scale using Na_2CO_3 and H_2O_2 in an acetone/H_2O mixture.[24][25] However, we observed longer reaction times and decreased yields on a larger scale. After extensive screening, best results in terms of conversion to both epoxy ketones **13** and **19** were obtained by a reagent combination of triton B and H_2O_2 in THF at 0°C, which led to formation of the two compounds in a combined yield of 78 % (**19**/**13** 5:2). The secondary hydroxy group of hydrolyzed epoxy ketone **13** was acetylated using standard reaction conditions (Ac_2O, NEt_3, DMAP) to give the acetoxy epoxide **20** in 88 % yield. With the aim to minimize the use of protecting groups, we continued by cyclizing the B-ring of epoxy ketone **20** and envisioned epoxide opening at a later stage. Unfortunately, neighboring group-assisted hydrolysis[14][15][26] on the octalone intermediate **17** resulted in formation of a complex mixture.



Scheme 3. Inversion of the hydroxy group at C3 in **14** by a Mitsunobu reaction, construction of the B-ring and attempted hydrolysis of the epoxide in **17**.

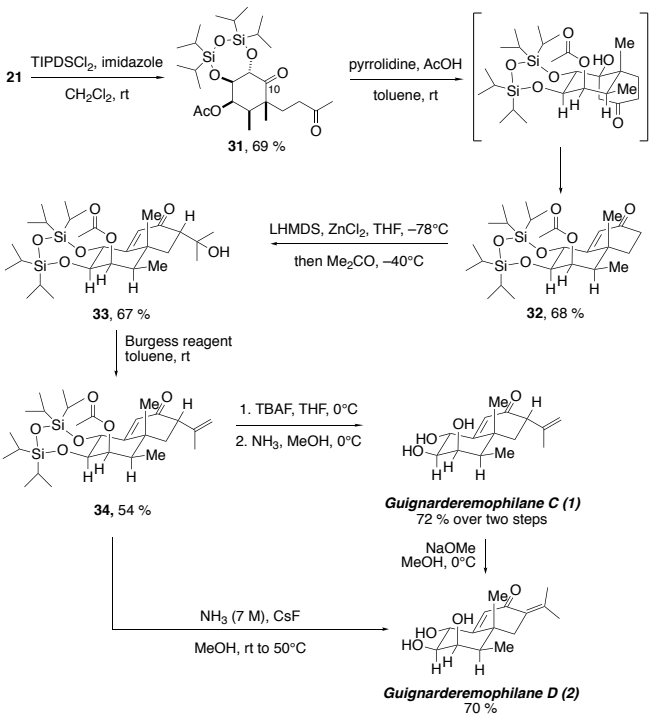
Therefore, we designed an approach with the aim to first complete the substitution pattern on the A-ring using protecting groups for the hydroxy functions at C1 and C2. Regioselective epoxide opening was triggered by treatment of **20** with the Lewis acid $BF_3{\cdot}OEt_2$ to form the desired triol **21** in 93 % yield (Scheme 4). Scaling up this reaction from 10 mg to >100 mg turned out to be problematic: the required reaction time was much longer (seven hours instead of two hours) and the yield dropped to 43 %. With **21** in hand, the next challenge was to find appropriate protecting groups for the *anti*-diol at C1 and C2. Ideally, these protecting groups would be cleavable under identical reaction conditions with respect to the conditions needed for cleavage of the acetyl group. Another aspect was to strive for very mild deprotection conditions as to avoid isomerization of the isopropenyl group to be installed in subsequent steps of the synthesis. Being aware that the C2 hydroxy function in β-position to the carbonyl group was prone to elimination, we initially investigated the introduction of acetyl and benzoyl protecting groups on the *anti*-diol at C1/C2. However, elimination of acetic acid or benzoic acid was observed in both the protection and the following aldol cyclization steps. Acetylation of **21** using Ac_2O, NEt_3 and DMAP furnished a mixture of the desired fully

acetylated triol **22** (44 %) and elimination product **23** (5:1). Benzoylation of **21** by BzCl, NEt_3 and DMAP gave only 22 % yield of the desired dibenzoylated product **24**. For both **22** and **24**, cyclization using pyrrolidine and AcOH resulted in partial elimination of the C2 acetyl (3:1 mixture of **25** and **26**) or C2 benzoyl (2:1 mixture of **27** and **28**) groups, respectively. Unsatisfactory results were also obtained for the cyclization attempts using the unprotected diol **21**, resulting in decomposition without formation of octalone **18**. Only mono-protection at either the C1 or the C2 hydroxy groups was observed in the reaction with TBSCl to form silyl ethers **29** and **30** (3:1) in a combined yield of 91 %. Attempted removal of the acetyl group at C3 with the goal to install silicon-based protecting groups for all three hydroxy substituents only gave a complex mixture instead of unprotected triol.



Scheme 4. A: Regioselective hydrolysis of the epoxide in **20**. **B**: Attempted strategies with protecting groups on the C1/C2 diol.

The reagent $TIPDSCl_2$, widely applied in carbohydrate chemistry for the protection of 1,2- and 1,3-diols,[27][28] was found suitable for our substrate, and the fully protected triol **31** was isolated in 69 % yield (Scheme 5). The following aldol condensation reaction with substrate **31** *via* an enamine intermediate generated by reaction with pyrrolidine in the presence of AcOH was successful (see Scheme 2), and both conversion and yield were further improved by changing the solvent from CH_2Cl_2 to the more apolar toluene to form octalone **32** in 68 % yield. Despite the steric demand of the TIPDS group and the imparted increase in rigidity of the A-ring due its fusion to an additional seven-membered silyloxy ring, intramolecular aldol addition to the ketone at C10 still took place. Studying the structure of the aldol addition intermediate (Scheme 5), it is discernible that the bottom face of the A-ring is not overly shielded from the TIPDS group in pseudo-equatorial orientation. Upon elimination of water, we now had octalone **32** in hand and addressed the installation of the isopropenyl group for targeting the sesquiterpene skeleton. Similar procedures on octalones using a two-step procedure have already been described in literature:[29 – 32] first, aldol addition to acetone gives the tertiary alcohol, which is then dehydrated regioselectively using Burgess reagent.[33 – 35] For the aldol step, we had to slightly modify the literature procedure and add the acetone to the enolate at –40°C, as previous experiments had shown no conversion and full recovery of starting material when the electrophile was added at –78°C. In case of our substrate, the seven-membered ring of the TIPDS group influences the conformation of the A- and B-ring and might thus lower the reactivity of the enolate formed by deprotonation of **32**. Upon modification of the known procedure, we isolated the desired tertiary alcohol **33** in an acceptable yield of 67 % with full diastereoselectivity.



Scheme 5. Construction of the B-ring and endgame in the synthesis of guignarderemophilanes C (**1**) and D (**2**).

To complete the installation of the three-carbon side chain, regio-selective elimination of water from **33** was achieved by treatment with Burgess reagent to give the isopropenylated octalone **34** as the desired elimination product in a modest yield of 54 %. Using triflic anhydride and DIPEA[32] instead of the milder Burgess reagent resulted in the formation of a complex mixture. Having all substituents installed, the endgame of the synthesis had to be addressed by deprotection of both the TIPDS and acetyl groups. With a combination of CsF and ammonia in methanol at 50°C,[36] all protecting groups were cleaved. However, formation of guignarderemophilane C (**1**) was not observed, as the alkaline reaction conditions turned out to effect isomerization of the C=C double bond of the isopropenyl group to provide guignarderemophilane D (**2**) instead. Therefore, in order to avoid isomerization and to give access to guignarderemophilane C (**1**), a milder two-step procedure was developed. Compound **34** was treated with TBAF as fluoride anion source to cleave the TIPDS group and after work-up, the acetyl group was removed by reaction with ammonia in methanol at room temperature. Both natural products were obtained after evaporation of the solvent and the ratio of the two natural product isomers slightly increased to 4.6:1 (**1**/**2**) in favor of **2** upon purification by flash column chromatography. Complete separation of the isomers was accomplished by reversed-phase HPLC

resulting in pure guignarderemophilane C (**1**) and guignarderemophilane D (**2**). Alternatively, guignarderemophilane D (**2**) was obtained from its isomer guignarderemophilane C (**1**) by treatment with NaOMe in MeOH at 0°C in 70 % yield. The NMR spectra (^{1}H and ^{13}C) of both the synthetic compounds were in agreement with those reported for the isolated natural products,[9] but for the optical rotation values we observed substantial differences and opposite signs for both compounds: our measured optical rotation value for guignarderemophilane C was $[\alpha]_D^{27}$ = +35° (c = 0.88, MeOH) and the reported value $[\alpha]_D^{20}$= –175° (c = 0.01, MeOH). The values for guignarderemophilane D were $[\alpha]_D^{27}$ = +38° (c = 0.70, MeOH) for the synthetic and $[\alpha]_D^{20}$ = –121° (c = 0.12, MeOH) for the isolated material. In order to provide evidence for the identity of the isolated natural products and the synthetic material, we measured a CD spectrum of synthesized **1**, which showed to be in agreement with the one reported in literature (see supporting information, figure S4).

Conclusion

In conclusion, we present the first total synthesis of the polyoxygenated eremophilane-type sesquiterpenes guignard-eremophilane C (**1**) and D (**2**) by applying a concise route starting from known intermediate **4**. Both syntheses have been achieved in eleven and ten steps, respectively. Installation of the three hydroxy groups in the A-ring was identified as a key challenge, which was successfully tackled by applying a Mitsunobu inversion, epoxidation and regioselective hydrolysis of the epoxide with neighboring-group participation. In order to find more potent neural anti-inflammatory active agents, derivatization of both the natural products and synthetic intermediates is envisioned.

Experimental Section

General Aspects and Materials

All chemicals have been purchased from Acros, Alfa Aesar, Fluorochem or Sigma-Aldrich and were used without further purification (except for Et_3N, which was freshly distilled before use). All reactions have been carried out in flame-dried glassware (unless aqueous reagents were used) and reactions involving air sensitive compounds have been performed under an argon or nitrogen atmosphere. Solvents applied for chemical transformations were either anhydrous quality or HPLC grade solvents, which have been dried by filtration through activated aluminum oxide under nitrogen (H_2O content <10 ppm, Karl-Fischer titration). For work-up and purification, solvents have been distilled from technical grade. All synthetic transformations have been monitored by either thin layer chromatography (TLC) or ^{1}H NMR spectroscopy. Yields refer to purified, dried and spectroscopically pure compounds. TLC was performed on Merck silica gel 60 F254 plates (0.25 mm thickness) pre-coated with a fluorescent indicator. Concentration under reduced pressure was performed by rotary evaporation at 40°C or by lyophilization. Flash chromatography was performed using silica gel 60 (230-400 mesh) from Sigma-Aldrich with a forced flow eluent at 0.1–0.3 bar pressure. High-performance liquid chromatography (HPLC) was performed by using an Agilent 1100 series instrument equipped with reversed-phase columns for analytical separation (Synergi Hydro-RP, 4 µm, 80 Å, 150 mm x 4.6 mm, Phenomenex) or semi-preparative separation (Synergi Hydro-RP, 10 µm, 80 Å, 150 mm x 10.0 mm, Phenomenex). All ^{1}H and ^{13}C NMR spectra were recorded using a Bruker 400 MHz (Avance II) or 500 MHz (Avance II or III) (^{1}H) & 101 MHz or 126 MHz (^{13}C) spectrometer at room temperature (unless otherwise stated). Chemical shifts (δ-values) are reported in ppm, spectra were calibrated relative to the residual proton chemical shifts ($CHCl_3$, δ = 7.26; MeOD-d_3, δ = 3.31) and carbon chemical shifts ($CDCl_3$, δ = 77.16; MeOD-d_4, δ = 49.00) of the solvents; multiplicity is reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved and coupling constant *J* is given in Hz. IR spectra were recorded on a Perkin Elmer SpectrumTwo ATR-FTIR. The absorptions are reported in cm^{-1}. All mass spectra (HRMS-ESI) were recorded by the Mass Spectrometric Service of the University of Zurich on a QExactive instrument (Thermo Fisher Scientific, Bremen, Germany) equipped with a heated electrospray (ESI) ionization source and connected to a Dionex Ultimate 3000 UHPLC system. Melting points (M.p.) were determined using a Büchi B-545 apparatus in open capillaries and are uncorrected. Optical rotations °$[\alpha]_D^T$ were measured at the sodium D line using a 1 mL cell with 1 dm path length, or a 0.2 mL cell with 0.1 dm path length on a Jasco P-2000 digital polarimeter and the concentration c is given in g/100 mL $CHCl_3$ or MeOH. CD spectra were acquired on a JASCO J-810 spectrometer.

(1a*R*,2*S*,3*R*,3a*R*,7b*R*)-2-((*tert*-butyldimethylsilyl)oxy)-3,3a-dimethyl-1a,3,3a,4,5,7b-hexahydronaphtho[1,2-*b*]oxiren-6(2*H*)-one (7): A mixture of α,β-epoxy ketone **8** (8.5 mg, 25 µmol, 1.0 eq.), pyrrolidine (4 µL, 50 µmol, 2.0 eq.) and acetic acid (3 µL, 50 µmol, 2.0 eq.) in CH_2Cl_2 (0.5 mL) was stirred for 2 h 20 min at rt, before it was quenched by addition of 0.1 M HCl and diluted with CH_2Cl_2. The layers were separated and the aqueous layer was extracted with Et_2O (3 x). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude material was subjected to flash column chromatography (pentane/Et_2O 3:1) to give the epoxy octalone **7** (5.9 mg, 18 µmol, 73 %) as a colorless solid.

M.p. = 76.2 – 77.5°C. TLC: R_f = 0.34 (SiO_2, pentane/Et_2O 1:1). $[\alpha]_D^{25}$ = +30.7° (c = 0.36, $CHCl_3$). FTIR (neat): $\tilde{\nu}$ = 2954, 2928, 2856, 1682, 1472, 1258, 1084, 855, 836, 775 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.14 (s, 1H), 3.89 (dd, *J* = 10.0, 1.8 Hz, 1H), 3.56 (d, *J* = 3.7 Hz, 1H), 3.46 (dd, *J* = 3.7, 1.8 Hz, 1H), 2.52 (ddd, *J* = 18.1, 14.1, 5.5 Hz, 1H), 2.47 – 2.40 (m, 1H), 1.97 (ddd, *J* = 13.4, 5.4, 2.3 Hz, 1H), 1.75 (td, *J* = 13.8, 5.5 Hz, 1H), 1.66 (dq, *J* = 10.0, 6.9 Hz, 1H), 1.04 (s, 3H), 0.96 (d, *J* = 7.0 Hz, 3H), 0.94 (s, 9H), 0.17 (s, 3H), 0.14 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 198.4, 161.2, 131.1, 71.4, 56.1, 54.7, 38.2, 37.7, 34.1, 33.5, 26.0, 18.3, 17.1, 9.7, -3.8, -4.4. HRMS (ESI) Exact mass calculated for $C_{18}H_{31}O_3Si^+$ $[M+H]^+$: 323.20370, found: 323.20360.

(1*S*,3*R*,4*R*,5*S*,6*R*)-5-((*tert*-butyldimethylsilyl)oxy)-3,4-dimethyl-3-(3-oxobutyl)-7-oxabicyclo[4.1.0]heptan-2-one (8) and (1*R*,3*R*,4*R*,5*S*,6*S*)-5-((*tert*-butyldimethylsilyl)oxy)-3,4-dimethyl-3-(3-oxobutyl)-7-oxabicyclo[4.1.0]heptan-2-one (9): To a solution of enone **4** (53.5 mg, 0.16 mmol, 1.0 eq.) in H_2O_2 (30 % in H_2O, 1.55 mL, 16.5 mmol, 100 eq.) and THF (3.0 mL) at 0°C was added Triton B (40 % in MeOH, 90 µL, 0.19 mmol, 1.2 eq). The reaction mixture was stirred for 5 h 45 min at that temperature and then quenched by addition of sat. aq. NH_4Cl solution. The aqueous mixture was extracted with Et_2O (3 x) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was subjected to flash column chromatography (pentane/Et_2O 5:1) to give the α,β-epoxy ketones **8** (26 mg, 76 µmol, 46 %) and **9** (8.3 mg, 0.024 mmol, 15 %) both as colorless oils.

α,β-Epoxy ketone 8: TLC: R_f = 0.34 (SiO_2, pentane/Et_2O 5:1). Optical rotation: $[\alpha]_D^{26}$ = –112.9° (c = 0.40, $CHCl_3$). FTIR (neat): $\tilde{\nu}$ = 2956, 2931, 2857, 1714, 1472, 1362, 1256, 1083, 860, 838, 776 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 3.90 (dd, *J* = 10.1, 1.0 Hz, 1H), 3.50 (d, *J* = 4.0 Hz, 1H), 3.31 (d, *J* = 4.0 Hz, 1H), 2.34 (ddd, *J* = 16.8, 11.5, 4.8 Hz, 1H), 2.21 (ddd, *J* = 17.4, 11.4, 4.7 Hz, 1H), 2.14 – 2.08 (m, 1H), 2.11 (s, 3H), 2.00 (ddd, J = 14.3, 11.5, 4.7 Hz, 1H), 1.65 (ddd, J = 14.3, 11.4, 4.9 Hz, 1H), 0.94 (s, 9H), 0.92 (s, 3H), 0.91 (d, J = 7.0 Hz, 3H), 0.16 (s, 3H), 0.13 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 208.1, 208.1, 70.6, 57.7, 55.5, 49.0, 38.6, 32.9, 30.1, 29.9, 25.9, 20.2, 18.2, 10.9, -3.9, -4.5. HRMS (ESI) Exact mass calculated for $C_{18}H_{33}O_4Si^+$ $[M+H]^+$: 341.21426, found: 341.21431.

α,β-Epoxy ketone 9: TLC: R_f = 0.40 (SiO_2, pentane/Et_2O 5:1). $[\alpha]_D^{25}$ = +14.6° (c = 0.26, $CHCl_3$). FTIR (neat): $\tilde{\nu}$ = 2955, 2930, 2894, 2858, 1712, 1258, 1084, 876, 837, 777 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 4.01 (d, *J* = 7.2 Hz, 1H), 3.44 (dd, *J* = 3.5, 0.7 Hz, 1H), 3.25 (dd, *J* = 3.6, 0.9 Hz, 1H), 2.38 (ddd, *J* = 16.3, 11.1, 4.8 Hz, 1H), 2.25 (ddd, *J* = 16.8, 11.0, 4.9 Hz, 1H), 2.13 (s, 3H), 1.99 (ddd, *J* = 14.3, 11.0, 4.9 Hz, 2H), 1.85 (p, *J* = 7.1 Hz, 1H), 1.66 (ddd, *J* = 14.3, 11.1, 4.9 Hz, 1H), 1.08 (s, 3H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.94 (s, 9H), 0.18 (s, 3H), 0.14 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 208.4 (2C), 70.4, 61.5, 54.1, 47.6, 44.0, 38.5, 30.5, 30.1, 25.9, 19.4, 18.2, 13.7, -4.3, -4.7. HRMS (ESI) Exact mass calculated for $C_{18}H_{33}O_4Si^+$ $[M+H]^+$: 341.21426 found: 341.21428.

(1a*S*,2*S*,3*R*,3a*R*,7b*S*)-2-((*tert*-butyldimethylsilyl)oxy)-3,3a-dimethyl-1a,3,3a,4,5,7b-hexahydronaphtho[1,2-*b*]oxiren-6(2*H*)-one (10): To a solution of TBS-protected enone **4** (21.0 mg, 65 µmol, 1.0 eq.) in THF (1.0 mL) at –10°C were added TBHP (5.5 M in decane, 59 µL, 0.32 mmol, 5.0 eq.) and Triton B (40 % in MeOH, 35 µL, 78 µmol, 1.2 eq.). The reaction mixture was stirred for 5 h and 15 min at –10°C and then quenched by addition of sat. aq. NH_4Cl solution. The aqueous mixture was extracted with Et_2O (3 x) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude material was purified twice by flash column chromatography (pentane/Et_2O 5:1) to give epoxy octalone **10** (8.2 mg, 25 µmol, 39 %) as a colorless solid.

M.p. = 107.4 – 110.1°C. TLC: R_f = 0.48 (SiO_2, pentane/Et_2O 5:1). $[\alpha]_D^{26}$ = –39° (c = 0.36, $CHCl_3$). FTIR (neat): $\tilde{\nu}$ = 2954, 2930, 2885, 2858, 1686, 1472, 1258, 1086, 1065, 865, 837, 776 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 6.16 (s, 1H), 3.76 (d, *J* = 9.9 Hz, 1H), 3.48 (d, *J* = 3.6 Hz, 1H), 3.44 (d, *J* = 3.6 Hz, 1H), 2.57 (ddd, *J* = 17.6, 14.9, 5.0 Hz, 1H), 2.41 (d, *J* = 17.4 Hz, 1H), 1.99 – 1.95 (m, 1H), 1.68 (td, *J* = 14.1, 4.5 Hz, 1H), 1.44 (dd, *J* = 9.8, 6.7 Hz, 1H), 1.15 (s, 3H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.94 (s, 9H), 0.19 (s, 3H), 0.14 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 198.3, 161.8, 129.6, 70.1, 61.9, 56.5, 47.7, 36.7, 35.8, 33.9, 25.9, 18.1, 17.2, 11.7, -4.1, -4.7. HRMS (ESI) Exact mass calculated for $C_{18}H_{31}O_3Si^+$ $[M+H]^+$: 323.20370, found: 323.20356.

(2*R*,3*R*,4*S*,5*R*)-4-((*tert*-butyldimethylsilyl)oxy)-5-hydroxy-2,3-dimethyl-2-(3-oxobutyl)cyclohexan-1-one (11): Stock solution: To a solution of diphenyl diselenide (89.5 mg, 287 mmol) in EtOH (1.0 mL) were added $NaBH_4$ (16.7 mg, 573 mmol) and acetic acid (4.0 µL), and the mixture was stirred at rt for 20 min to form a yellow solution.

α,β-Epoxy ketone **8** (13.0 mg, 38.0 µmol, 1.0 eq.) was dissolved in CH_2Cl_2 (0.2 mL) and the prepared stock solution (0.2 mL, 57 µmol, 1.5 eq) was added over a period of 5 min at rt. The reaction mixture turned yellow and was stirred for 1 h 10 min, before it was diluted with CH_2Cl_2 and brine. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was subjected to flash column chromatography (pentane/Et_2O 1:1) to give the β-hydroxy ketone **11** (5.6 mg, 16 µmol, 43 %) as a colorless oil.

TLC: R_f = 0.50 (SiO_2, pentane/Et_2O 1:3). $[\alpha]_D^{26}$ = +21.8° (c = 0.28, $CHCl_3$). FTIR (neat): $\tilde{\nu}$ = 3493, 2955, 2929, 2857, 1711, 1463, 1254, 1067, 837, 776 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 4.08 (q, *J* = 3.4 Hz, 1H), 3.82 (dd, *J* = 10.0, 2.7 Hz, 1H), 2.69 (ddd, *J* = 15.3, 3.4, 2.2 Hz, 1H), 2.57 (dd, *J* = 15.4, 3.6 Hz, 1H), 2.50 (ddd, *J* = 17.3, 11.2, 4.5 Hz, 1H), 2.40 (dd, *J* = 2.2, 1.0 Hz, 1H), 2.28 (ddd, *J* = 16.9, 11.1, 4.9 Hz, 1H), 2.17 – 2.08 (m, 1H), 2.14 (s, 3H), 1.97 (ddd, *J* = 14.3, 11.2, 4.5 Hz, 1H), 1.04 (s, 3H), 1.61 (ddd, *J* = 14.2, 11.1, 4.9 Hz, 1H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.93 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 212.0, 209.0, 74.2, 71.5, 50.2, 42.5, 38.8, 36.4, 30.2, 28.7, 26.0, 20.6, 18.2, 11.7, -4.1, -4.4. HRMS (ESI) Exact mass calculated for $C_{18}H_{35}O_4Si^+$ $[M+H]^+$: 343.22991, found: 343.22956.

(1*S*,3*R*,4*R*,5*S*,6*S*)-5-hydroxy-3,4-dimethyl-3-(3-oxobutyl)-7-oxabicyclo[4.1.0]heptan-2-one (12): To a solution of α,β-epoxy ketone **8** (9.0 mg, 26 µmol, 1.0 eq.) in MeCN (0.5 mL) was added HF (48 % in H_2O, 5 µL, 0.26 mmol, 10 eq.). The mixture was stirred for 3 h 15 min at rt before it was quenched by addition of sat. aq. $NaHCO_3$. The mixture was extracted with Et_2O (3 x) and the combined organic layers were washed with H_2O, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (pentane/Et_2O 1:3 to 1:5 to 1:7) to afford the epoxy alcohol **12** (3.9 mg, 17 µmol, 65 %) as a colorless oil.

TLC: R_f = 0.50 (SiO_2, Et_2O). ^1H NMR (400 MHz, $CDCl_3$) δ = 3.89 (ddd, *J* = 10.0, 8.6, 1.2 Hz, 1H), 3.67 (dd, *J* = 4.0, 1.1 Hz, 1H), 3.39 (d, *J* = 4.0 Hz, 1H), 2.40 – 2.18 (m, 2H), 2.12 (s, 3H), 2.09 – 1.94 (m, 2H), 1.78 (d, *J* = 8.6 Hz, 1H), 1.66 (ddd, *J* = 14.3, 10.5, 5.6 Hz, 1H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.94 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 207.9, 207.2, 70.2, 57.3, 55.6, 49.1, 38.6, 33.3, 30.1, 29.4, 20.0, 10.4. HRMS (ESI) Exact mass calculated for $C_{12}H_{18}O_4Na^+$ $[M+Na]^+$: 249.10973, found: 249.10979.

(4*R*,5*R*,6*R*)-4-hydroxy-5,6-dimethyl-6-(3-oxobutyl)cyclohex-2-en-1-one (14): To a solution of TBS protected alcohol **4** (792 mg, 2.44 mmol, 1.0 eq.) in MeCN (36 mL) was added HF (48 % in H_2O, 1.0 mL, 24.4 mmol, 10 eq.). The mixture was stirred for 38 h at rt, before it was quenched by addition of sat. aq. $NaHCO_3$. The solution was extracted with Et_2O (3 x) and the combined organic layers were washed with H_2O, dried over Na_2SO_4, filtered and concentrated. The crude material was subjected to flash column chromatography (Et_2O) to yield the allylic alcohol **14** (471 mg, 2.24 mmol, 92 %) as a colorless solid.

M.p. = 78.8 – 83.5°C. TLC: R_f = 0.38 (SiO_2, Et_2O). $[\alpha]_D^{26}$ = –63.6° (c = 0.48, $CHCl_3$). FTIR (neat): $\tilde{\nu}$ = 3472, 2971, 2020, 1713, 1672, 1377, 1041 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 6.82 (dd, *J* = 10.3, 2.0 Hz, 1H), 5.92 (dd, *J* = 10.2, 2.2 Hz, 1H), 4.22 (ddt, *J* = 9.4, 7.2, 2.1 Hz, 1H), 2.33 (ddd, *J* = 15.1, 11.3, 4.2 Hz, 1H), 2.27 – 2.19 (m, 1H), 2.19 – 2.09 (m, 1H), 2.14 (s, 3H), 1.96 (dq, *J* = 9.5, 6.7 Hz, 1H), 1.84 (d, *J* = 7.2 Hz, 1H), 1.62 (ddd, *J* = 14.0, 11.3, 4.1 Hz, 1H), 1.11 (d, *J* = 6.8 Hz, 3H), 1.02 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 208.8, 203.2, 150.7, 127.9, 70.6, 48.5, 42.8, 38.5, 30.0, 28.4, 19.3, 10.8. HRMS (ESI) Exact mass calculated for $C_{12}H_{19}O_3^+$ $[M+H]^+$: 211.13287, found: 211.13286.

(1*S*,5*R*,6*R*)-5,6-dimethyl-4-oxo-5-(3-oxobutyl)cyclohex-2-en-1-yl 4-nitrobenzoate (15): Triphenylphosphine (517 mg, 1.95 mmol, 2.0 eq.) and DIAD (383 µL, 1.95 mmol, 2.0 eq.) were dissolved in THF (4.5 mL) at 0°C. After 5 min allylic alcohol **14** (205 mg, 0.98 mmol, 1.0 eq.) in THF (7.5 mL) and 4-nitrobenzoic acid (329 mg, 1.95 mmol, 2.0 eq.) were added to the reaction mixture. After stirring was continued for 5 min at 0°C, the reaction mixture was allowed to warm up to rt and was stirred for 35 min, before it was heated to 60°C for 1 h in the microwave. After evaporation of the solvent, the crude material was subjected to flash column chromatography (pentane/Et_2O 1:1) to give the ester **15** (345 mg, 0.98 mmol, quant.) as a colorless solid.

M.p. = 72.6 – 74.6°C. TLC: R_f = 0.25 (SiO_2, pentane/Et_2O 1:1). $[\alpha]_D^{26}$ = +159.2° (c = 0.47, $CHCl_3$). FTIR (neat): $\tilde{\nu}$ = 2982, 1723, 1682, 1528, 1348, 1270, 1102, 1066 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 8.34 – 8.29 (m, 2H), 8.24 – 8.20 (m, 2H), 6.74 (ddd, *J* = 10.2, 2.9, 1.5 Hz, 1H), 6.09 (dt, *J* = 5.1, 2.6 Hz, 1H), 6.06 (dd, *J* = 10.2, 2.1 Hz, 1H), 2.59 – 2.52 (m, 2H), 2.37 (ddd, *J* = 17.5, 10.5, 5.2 Hz, 1H), 2.17 (s, 3H), 2.02 (ddd, *J* = 14.4, 10.5, 5.3 Hz, 1H), 1.93 (ddd, *J* = 14.4, 10.6, 5.2 Hz, 1H), 1.16 (s, 3H), 1.03 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 207.7, 202.3, 164.0, 150.9, 142.6, 135.0, 130.9, 130.0, 123.9, 71.7, 49.2, 40.8, 38.4, 30.2, 29.6, 19.9, 10.1. HRMS (ESI) Exact mass calculated for $C_{19}H_{21}NO_6Na^+$ $[M+Na]^+$: 382.12611, found: 382.12626.

(1*R*,2*S*,8a*R*)-1,8a-dimethyl-6-oxo-1,2,6,7,8,8a-hexahydro-naphthalen-2-yl 4-nitrobenzoate (16): A mixture of ester **15** (14.1 mg, 39 µmol, 1.0 eq.), pyrrolidine (6 µL, 78 µmol, 2.0 eq.) and acetic acid (4.5 µL, 78 µmol, 2.0 eq.) in CH_2Cl_2 (0.4 mL) was stirred for 3 h 10 min at rt, before additional pyrrolidine (2.0 eq.) and acetic acid (2.0 eq.) were added. After in total 9 h at rt the mixture was quenched by addition of 0.1 M HCl and diluted with CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Since the residue still contained enone **15** (monitored by ^1H NMR), a mixture of crude material, pyrrolidine (2.0 eq.) and acetic acid (2.0 eq.) in CH_2Cl_2 (0.5 mL) was stirred for additional 14 h. The same work-up procedure was carried out as described before and the obtained residue was subjected to flash column chromatography (pentane/Et_2O 1:1) to give the dienone **16** (8.1 mg, 39.2 µmol, 61 %) as a colorless solid.

M.p. = 162.3 – 163.6°C. TLC: R_f = 0.54 (SiO_2, pentane/Et_2O 1:2). $[\alpha]_D^{26}$ = +699° (c = 0.41, $CHCl_3$). FTIR (neat): $\tilde{\nu}$ = 3111, 2971, 2944, 1721, 1663, 1527, 1268, 1093, 719 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 8.31 (d, *J* = 8.7 Hz, 2H), 8.18 (d, *J* = 8.6 Hz, 2H), 6.41 (d, *J* = 9.7 Hz, 1H), 6.33 (dd, *J* = 9.7, 5.2 Hz, 1H), 5.85 (s, 1H), 5.64 (t, *J* = 4.9 Hz, 1H), 2.61 (ddd, *J* = 18.0, 14.2, 5.4 Hz, 1H), 2.52 (ddd, *J* = 18.0, 5.3, 2.1 Hz, 1H), 2.14 (ddd, *J* = 13.4, 5.4, 2.2 Hz, 1H), 2.08 (dd, *J* = 7.2, 4.7 Hz, 1H), 1.81 (td, *J* = 13.8, 5.2 Hz, 1H), 1.41 (s, 3H), 1.12 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 199.2, 164.5, 160.7, 150.8, 135.5, 132.4, 131.4, 130.8, 126.6, 123.9, 71.5, 41.1, 35.8, 34.3, 34.1, 18.4, 10.5. HRMS (ESI) Exact mass calculated for $C_{19}H_{20}NO_5^+$ $[M+H]^+$: 342.13360, found: 342.13368.

(1a*S*,2*R*,3*R*,3a*R*,7b*R*)-3,3a-dimethyl-6-oxo-1a,2,3,3a,4,5,6,7b-octahydronaphtho[1,2-*b*]oxiren-2-yl acetate (17): A mixture of α,β-epoxy ketone **20** (19.3 mg, 72 µmol, 1.0 eq), pyrrolidine (12 µL, 0.14 mmol, 2.0 eq.) and acetic acid (8.2 µL, 0.14 mmol, 2.0 eq) in CH_2Cl_2 (0.6 mL) was stirred at rt overnight. The mixture was quenched by addition of 0.1 M HCl and diluted with CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude residue was subjected to flash column chromatography (pentane/Et_2O 1:1) to yield epoxy octalone **17** (14.2 mg, 57 µmol, 79 %) as a colorless solid.

M.p. = 81.8 – 85.8°C. TLC: R_f = 0.44 (SiO_2, pentane/Et_2O 1:1). $[\alpha]_D^{23}$ = +212.6° (c = 0.62, $CHCl_3$). FTIR (neat): $\tilde{\nu}$ = 2923, 2853, 1744, 1681, 1374, 1230, 1026 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 6.17 (s, 1H), 5.42 – 5.39 (m, 1H), 3.56 (d, *J* = 3.3 Hz, 1H), 3.50 (dd, *J* = 3.3, 2.1 Hz, 1H), 2.60 (ddd, *J* = 18.3, 14.1, 5.6 Hz, 1H), 2.52 – 2.42 (m, 1H), 2.15 (s, 3H), 1.99 (ddd, *J* = 13.3, 5.4, 2.2 Hz, 1H), 1.87 (qd, *J* = 7.3, 3.9 Hz, 1H), 1.71 (td, *J* = 13.7, 5.4 Hz, 1H), 1.21 (s, 3H), 0.94 (d, *J* = 7.2 Hz,

3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 198.1, 170.4, 160.6, 131.7, 70.8, 53.0, 53.0, 35.6, 34.7, 34.1, 34.0, 21.1, 18.8, 9.8. HRMS (ESI) Exact mass calculated for $C_{14}H_{19}O_4^+$ $[M+H]^+$: 251.12779, found: 251.12786.

(1*S*,2*R*,3*R*,4*R*,6*S*)-3,4-dimethyl-5-oxo-4-(3-oxobutyl)-7-oxabicyclo[4.1.0]heptan-2-yl 4-nitrobenzoate (13) and (1*S*,3*R*,4*R*,5*R*,6*S*)-5-hydroxy-3,4-dimethyl-3-(3-oxobutyl)-7-oxabicyclo[4.1.0]heptan-2-one (19): Ester **15** (25.6 mg, 71 µmol, 1.0 eq.) was dissolved in THF (1.5 mL) and cooled to 0°C. Hydrogen peroxide (30 % in H_2O, 675 µL, 7.12 mmol, 100 eq.) and Triton B (40 % in MeOH, 32 µL, 71 µmol, 1.0 eq.) were added and the reaction mixture was stirred for 2 h 40 min at 0°C, before it was quenched by addition of sat. aq. Na_2CO_3 and diluted with Et_2O. The layers were separated and the aqueous layer was extracted with Et_2O (3 x). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude residue was subjected to flash column chromatography (Et_2O/pentane 2:1) to give the epoxy ester **13** (5.80 mg, 15 µmol, 22 %) as a colorless solid and epoxy alcohol **19** (9.0 mg, 40 µmol, 56 %) as a colorless oil.

Epoxy ester 13: M.p. = 112.2 – 113.9°C. TLC: R_f = 0.43 (SiO_2, pentane/Et_2O 1:1). $[\alpha]_D^{24}$ = +27.9° (c = 0.29, $CHCl_3$). FTIR (neat): $\tilde{\nu}$ = 2919, 1714, 1528, 1348, 1266, 1099, 718 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.31 (d, *J* = 8.8 Hz, 2H), 8.15 – 8.12 (m, 2H), 5.74 (t, *J* = 3.0 Hz, 1H), 3.85 (t, *J* = 3.6 Hz, 1H), 3.45 (d, *J* = 4.0 Hz, 1H), 2.56 (qd, *J* = 7.3, 2.9 Hz, 1H), 2.48 – 2.32 (m, 2H), 2.15 (s, 3H), 1.95 (ddd, *J* = 15.4, 9.9, 5.6 Hz, 1H), 1.86 (ddd, *J* = 14.7, 9.9, 5.8 Hz, 1H), 1.19 (s, 3H), 1.04 (d, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 208.8, 207.7, 164.5, 151.0, 134.6, 131.0, 124.0, 74.2, 55.1, 54.4, 48.1, 38.4, 33.5, 31.8, 30.3, 21.2, 11.8. HRMS (ESI) Exact mass calculated for $C_{19}H_{21}O_7NNa^+$ $[M+Na]^+$: 398.12102, found: 398.12103.

Epoxy alcohol 19: TLC: R_f = 0.27 (SiO_2, pentane/Et_2O 1:1). $[\alpha]_D^{25}$ = –65.5° (c = 0.20, $CHCl_3$). FTIR (neat): $\tilde{\nu}$ = 3481, 2917, 2849, 1700, 1369, 1259, 1167 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.34 (d, *J* = 3.9 Hz, 1H), 3.64 (t, *J* = 3.6 Hz, 1H), 3.36 (d, *J* = 3.9 Hz, 1H), 2.38 (ddd, *J* = 16.4, 10.5, 5.4 Hz, 1H), 2.33 – 2.25 (m, 1H), 2.17 (qd, *J* = 7.4, 2.7 Hz, 1H), 2.12 (s, 3H), 2.04 (d, *J* = 4.6 Hz, 1H), 1.85 (ddd, *J* = 13.9, 10.5, 5.3 Hz, 1H), 1.74 (ddd, *J* = 14.0, 10.4, 5.4 Hz, 1H), 1.09 (s, 3H), 1.03 (dd, *J* = 7.3, 1.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 209.9, 208.4, 70.6, 57.0, 54.9, 48.0, 38.7, 33.8, 31.7, 30.2, 21.8, 11.5. HRMS (ESI) Exact mass calculated for $C_{12}H_{19}O_4^+$ $[M+H]^+$: 227.12779, found: 227.12784.

(1*S*,2*R*,3*R*,4*R*,6*S*)-3,4-dimethyl-5-oxo-4-(3-oxobutyl)-7-oxabicyclo[4.1.0]heptan-2-yl acetate (20): To a solution of epoxy alcohol **19** (102 mg, 0.45 mmol, 1.0 eq.) in CH_2Cl_2 (4.0 mL) was added Et_3N (127 µL, 0.90 mmol, 2.0 eq.), Ac_2O (169 µL, 1.8 mmol, 4.0 eq.) and DMAP (5.5 mg, 0.045 mmol, 0.1 eq.). The resulting mixture was stirred at rt for 1 h, then quenched by addition of 0.1 M HCl and diluted with CH_2Cl_2. After the layers were separated, the aqueous layer was extracted with CH_2Cl_2 (3 x). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude material was subjected to flash column chromatography (pentane/Et_2O 1:1) to afford acetate **20** (107 mg, 0.45 mmol, 88 %) as a colorless solid.

M.p. = 71.8 – 73.9°C. TLC: R_f = 0.45 (SiO_2, pentane/Et_2O 1:1). $[\alpha]_D^{25}$ = –14.5° (c = 0.23, $CHCl_3$). FTIR (neat): $\tilde{\nu}$ = 2918, 2849, 1745, 1700, 1462, 1369, 1227, 1016, 977 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.43 (t, *J* = 3.1 Hz, 1H), 3.72 – 3.68 (m, 1H), 3.36 (d, *J* = 3.9 Hz, 1H), 2.46 – 2.26 (m, 3H), 2.13 (s, 3H), 2.10 (s, 3H), 1.88 (ddd, *J* = 14.3, 10.1, 5.5 Hz, 1H), 1.77 (ddd, *J* = 14.3, 10.2, 5.7 Hz, 1H), 1.08 (s, 3H), 0.95 (d, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = (126 MHz, $CDCl_3$) δ = 209.3, 207.9, 170.6, 72.3, 55.0, 54.5, 48.1, 38.5, 32.7, 31.8, 30.2, 21.2, 20.9, 11.5. HRMS (ESI) Exact mass calculated for $C_{14}H_{20}O_5Na^+$ $[M+Na]^+$: 291.12029, found: 291.12025.

(1*R*,2*R*,3*R*,5*S*,6*S*)-5,6-dihydroxy-2,3-dimethyl-4-oxo-3-(3-oxobutyl)cyclohexyl acetate (21): A solution of epoxy ketone **20** (108 mg, 0.40 mmol, 1.0 eq.) in toluene (4.5 mL) was cooled to 0°C and $BF_3{\cdot}Et_2O$ (56.2 µL, 0.44 mmol, 1.1 eq.) was added. The resulting yellow solution was stirred for 7 h and then quenched by addition of sat. aq. $NaHCO_3$. The mixture was extracted with EtOAc (3 x) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude material was subjected to flash column chromatography (EtOAc) to give the 1,2-diol **21** (50.4 mg, 0.40 mmol, 44 %) as a colorless oil.

TLC: R_f = 0.25 (SiO_2, EtOAc). $[\alpha]_D^{24}$ = –1.5° (c = 0.21, $CHCl_3$). FTIR (neat): $\tilde{\nu}$ = 3453, 2918, 2848, 1743, 1713, 1375, 1238, 1103, 1005 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.50 (t, *J* = 3.3 Hz, 1H), 4.60 (d, *J* = 10.8 Hz, 1H), 3.59 (dd, *J* = 10.8, 3.4 Hz, 1H), 3.52 (brs, 1H), 2.58 (brs, 1H), 2.47 – 2.28 (m, 2H), 2.19 (s, 3H), 2.16 (s, 3H), 2.01 (ddd, *J* = 15.2, 10.3, 5.3 Hz, 1H), 1.88 (qd, *J* = 7.0, 3.1 Hz, 1H), 1.65 (ddd, *J* = 14.5, 10.4, 5.3 Hz, 1H), 1.26 (s, 3H), 1.04 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 211.9, 208.1, 170.8, 75.5, 73.9, 73.9, 49.5, 38.9, 36.2, 30.2, 29.2, 21.3, 21.1, 10.9. HRMS (ESI) Exact mass calculated for $C_{14}H_{22}O_6Na^+$ $[M+Na]^+$: 309.13086, found: 309.13086.

(1*S*,2*R*,3*R*,4*R*,5*R*)-4,5-dimethyl-6-oxo-5-(3-oxobutyl)cyclohexane-1,2,3-triyl triacetate (22): To a solution of 1,2-diol **21** (3.9 mg, 14 µmol, 1.0 eq.) in CH_2Cl_2 (0.3 mL) was added Et_3N (6 µL, 41 µmol, 3.0 eq.), Ac_2O (9 µL, 95 µmol, 7.0 eq.) and DMAP (0.3 mg, 2.7 µmol, 0.2 eq.) at rt. The resulting mixture was stirred at rt for 1 h, then quenched by addition of a 0.1 M HCl solution and diluted with CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude material was subjected to flash column chromatography (pentane/Et_2O 1:2) to afford the tri-acetylated compound **22** (2.2 mg, 6.0 µmol, 44 %) as a colorless oil.

TLC: R_f = 0.39 (SiO_2, pentane/Et_2O 1:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.72 (d, *J* = 12.0 Hz, 1H), 5.55 (t, *J* = 3.2 Hz, 1H), 5.08 (dd, *J* = 12.0, 3.4 Hz, 1H), 2.42 (ddd, *J* = 16.3, 10.7, 5.1 Hz, 1H), 2.36 – 2.26 (m, 1H), 2.19 (s, 3H), 2.17 (s, 3H), 2.15 (s, 3H), 2.02 (s, 3H), 2.00 – 1.91

(m, 2H), 1.62 (ddd, *J* = 14.5, 10.6, 5.2 Hz, 1H), 1.30 (s, 3H), 1.03 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 208.0, 204.3, 170.3, 170.2, 169.8, 72.9, 72.5, 71.2, 50.6, 38.8, 35.3, 30.1, 29.3, 21.0, 21.0, 20.8, 20.7, 10.8. HRMS (ESI) Exact mass calculated for $C_{18}H_{26}O_8Na^+$ $[M+Na]^+$: 393.15199, found: 393.15203.

(1*R*,2*S*,4*R*,5*R*,6*R*)-6-acetoxy-4,5-dimethyl-3-oxo-4-(3-oxobutyl)-cyclohexane-1,2-diyl dibenzoate (24): To a solution of 1,2-diol **21** (3.7 mg, 13 µmol, 1.0 eq.) in CH_2Cl_2 (0.3 mL) was added Et_3N (3.7 µL, 26 µmol, 2.0 eq.), BzCl (6.0 µL, 52 µmol, 4.0 eq.) and DMAP (0.15 mg, 1.3 µmol, 0.1 eq.) at 0°C. The reaction mixture was allowed to warm up to rt and stirred for 2 h 15 min, before additional BzCl (20 µL, 0.17 mmol, 13 eq.) was added. After stirring for 19 h at rt, additional Et_3N (7 µL, 52 µmol, 4.0 eq.) was added to the mixture and the solvent was evaporated after the mixture was stirred for in total 23 h 15 min. The residue was subjected to flash column chromatography (SiO_2, pentane/Et_2O 1:1) to afford the dibenzylated product **24** (1.4 mg, 3 µmol, 22 %) as a colorless solid.

M.p. = 131.3 – 134.4°C. TLC: R_f = 0.34 (SiO_2, pentane/Et_2O, 1:1). $[\alpha]_D^{24}$ = –39.0° (c = 1.10, $CHCl_3$). FTIR (neat): $\tilde{\nu}$ = 2926, 1720, 1452, 1267, 1224, 1094, 710 cm^{-1}. ^{1}H NMR (500 MHz, Chloroform-*d*) δ = 8.04 – 7.99 (m, 2H), 7.93 – 7.88 (m, 2H), 7.56 – 7.51 (m, 2H), 7.43 – 7.36 (m, 4H), 6.17 (d, *J*=11.9, 1H), 5.78 (t, *J*=3.3, 1H), 5.56 (dd, *J*=11.9, 3.5, 1H), 2.49 (ddd, *J*=16.1, 10.8, 4.9, 1H), 2.38 (ddd, *J*=16.8, 10.6, 5.0, 1H), 2.22 (s, 3H), 2.15 (s, 3H), 2.10 (qd, *J*=7.2, 3.3, 1H), 2.04 (td, *J*=10.3, 5.3, 1H), 1.68 (ddd, *J*=14.4, 10.7, 5.0, 1H), 1.42 (s, 3H), 1.10 (d, *J*=6.9, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 208.2, 204.1, 170.0, 165.9, 165.4, 133.6 (2C), 130.0 (2C), 129.8 (2C), 129.2, 129.1, 128.6 (2C), 128.6 (2C), 73.7, 72.6, 71.8, 50.7, 38.9, 35.7, 30.2, 29.4, 21.0 (2C), 10.9. HRMS (ESI) Exact mass calculated for $C_{28}H_{30}O_8Na^+$ $[M+H]^+$: 517.18328, found: 517.18333.

(1*R*,2*R*,3*R*,5*S*,6*R*)-5-((*tert*-butyldimethylsilyl)oxy)-6-hydroxy-2,3-dimethyl-4-oxo-3-(3-oxobutyl)cyclohexyl acetate (29) and (1*R*,2*R*,3*R*,5*S*,6*S*)-6-((*tert*-butyldimethylsilyl)oxy)-5-hydroxy-2,3-dimethyl-4-oxo-3-(3-oxobutyl)cyclohexyl acetate (30): To a solution of 1,2-diol **21** (22.3 mg, 78 µmol, 1.0 eq), imidazole (13.3 mg, 0.20 mmol, 2.5 eq) and DMAP (4.8 mg, 39 µmol 0.5 eq.) in CH_2Cl_2 (0.9 mL) was added TBSCl (47.5 mg, 0.31 µmol, 4.0 eq) and the mixture was stirred at rt for 15 h. The reaction mixture was quenched by addition of sat. aq. NH_4Cl solution, and extracted with CH_2Cl_2 (3 x). The combined organic layers were washed with H_2O and brine, dried over Na_2SO_4 and concentrated. The crude material was subjected to flash column chromatography (pentane/Et_2O, 1:2) to afford the silyl ether **29** (20.8 mg, 51.9 µmol, 67 %) as a colorless oil and impure **30**. After a second flash column chromatography (pentane/Et_2O 4:1 to 2:1 to 1:1) silyl ether **30** (7.5 mg, 18.7 µmol, 24 %) was obtained as a colorless solid.

TBS ether 29: TLC: R_f = 0.21 (SiO_2, pentane/Et_2O 1:2). $[\alpha]_D^{23}$ = –31.7° (c = 0.99, $CHCl_3$). FTIR (neat): $\tilde{\nu}$ = 3483, 2930, 2857, 1747, 1711, 1234, 1126, 1007, 839, 781 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.55 (t, *J*=3.3, 1H), 4.66 (d, *J*=10.7, 1H), 3.67 (ddd, *J*=10.7, 3.3, 1.3, 1H), 2.46 (ddd, *J*=17.0, 11.0, 4.7, 1H), 2.39 (s, 1H), 2.26 (ddd, *J*=16.9, 11.0, 5.0, 1H), 2.17 (s, 3H), 2.14 (s, 3H), 1.95 (ddd, *J*=14.4, 11.0, 4.7, 1H), 1.85 (qd, *J*=7.0, 3.2, 1H), 1.57 (ddd, *J*=14.4, 11.0, 5.0, 1H), 1.21 (s, 3H), 1.00 (d, *J*=7.1, 3H), 0.93 (s, 9H), 0.18 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 210.0, 208.4, 170.6, 75.9, 74.2, 73.9, 50.5, 38.9, 35.5, 30.1, 29.3, 26.0, 21.8, 21.1, 18.8, 10.8, -4.3, -5.5. HRMS (ESI) Exact mass calculated for $C_{20}H_{37}O_6Si^+$ $[M+H]^+$: 401.23539, found: 401.23538 and for $C_{20}H_{36}O_6SiNa^+$ $[M+Na]^+$: 423.21734, found: 423.21699.

TBS ether 30: M.p. = 97.1 – 99.3°C. TLC: R_f = 0.65 (SiO_2, pentane/Et_2O 1:2). $[\alpha]_D^{24}$ = –7.1° (c = 0.31, $CHCl_3$). FTIR (neat): $\tilde{\nu}$ = 3492, 2930, 2857, 1746, 1720, 1372, 1237, 1165, 1010, 838, 781 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.37 (t, *J*=3.3, 1H), 4.56 (dd, *J*=10.4, 3.9, 1H), 3.50 (dd, *J*=10.4, 3.6, 1H), 3.43 (d, *J*=4.0, 1H), 2.42 (ddd, *J*=16.1, 10.7, 5.1, 1H), 2.34 (ddd, *J*=16.9, 10.6, 5.2, 1H), 2.16 (s, 3H), 2.14 (s, 3H), 1.99 (ddd, *J*=14.4, 10.5, 5.0, 1H), 1.81 (qd, *J*=7.0, 3.1, 1H), 1.63 (ddd, *J*=14.4, 10.7, 5.2, 1H), 1.23 (s, 3H), 1.01 (d, *J*=7.0, 3H), 0.87 (s, 9H), 0.12 (s, 3H), 0.07 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 212.8, 208.2, 170.3, 76.3, 75.2, 74.5, 49.3, 38.9, 35.8, 30.2, 29.3, 25.7, 21.1 (2C), 18.3, 10.8, -4.5, -5.0. HRMS (ESI) Exact mass calculated for $C_{20}H_{36}O_6SiNa^+$ $[M+Na]^+$: 423.21734, found: 423.21744.

(5a*R*,6*R*,7*R*,8*R*,9a*S*)-2,2,4,4-tetraisopropyl-7,8-dimethyl-9-oxo-8-(3-oxobutyl)hexahydrobenzo[*f*][1,3,5,2,4]trioxadisilepin-6-yl acetate (31): 1,2-Diol **21** (50.4 mg, 0.18 mmol, 1.0 eq.) was dissolved in CH_2Cl_2 (1.0 mL), before imidazole (48.0 mg, 0.70 mmol, 4.0 eq.) and $TIPDSCl_2$ (67 µL, 0.21 mmol, 1.2 eq.) were added. The turbid mixture was stirred for 9 h 15 min, before it was diluted by addition of sat. aq. NH_4Cl solution and CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x). The combined organic layers were washed with H_2O and brine, dried over Na_2SO_4, filtered and concentrated. The residue was subjected to flash column chromatography (pentane/Et_2O 2:1) to afford fully protected triol **31** (64.1 mg, 0.12 mmol, 69 %) as a colorless oil.

TLC: R_f = 0.67 (SiO_2, pentane/Et_2O 1:1). $[\alpha]_D^{22}$ = +10.2° (c = 0.57, $CHCl_3$). FTIR (neat): $\tilde{\nu}$ = 3514, 2945, 2867, 1755, 1727, 1464, 1367, 1234, 1165, 1054, 985 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 5.50 (t, *J* = 3.5 Hz, 1H), 4.79 (d, *J* = 10.1 Hz, 1H), 3.82 (dd, *J* = 10.2, 3.7 Hz, 1H), 2.47 (ddd, *J* = 16.1, 11.1, 4.6 Hz, 1H), 2.31 (ddd, *J* = 16.6, 11.1, 4.9 Hz, 1H), 2.14 (s, 3H), 2.13 (s, 3H), 1.97 (ddd, *J* = 15.3, 11.1, 4.5 Hz, 1H), 1.83 (qd, *J* = 7.0, 3.0 Hz, 1H), 1.56 (ddd, *J* = 14.4, 11.1, 4.9 Hz, 1H), 1.21 (s, 3H), 1.11-0.96 (m, 31H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 208.6, 208.4, 170.2, 76.7, 76.6, 74.8, 50.0, 39.0, 35.3, 30.1, 29.6, 21.4, 21.1, 17.6 – 17.1 (8C), 13.0, 12.9, 12.8, 12.1, 10.9. HRMS (ESI) Exact mass calculated for $C_{26}H_{49}O_7Si_2^+$ $[M+H]^+$: 529.30113, found: 529.30172 and for $C_{26}H_{48}O_7Si_2Na^+$ $[M+Na]^+$: 551.28308, found: 551.28343.

(5a*R*,6*R*,7*R*,7a*R*,11b*R*)-2,2,4,4-tetraisopropyl-7,7a-dimethyl-10-oxo-5a,6,7,7a,8,9,10,11b-octahydronaphtho[1,2-*f*][1,3,5,2,4]tri-

oxadisilepin-6-yl acetate (32): A mixture of fully protected triol **31** (64 mg, 0.12 mmol, 1.0 eq.), pyrrolidine (20 µL, 0.24 mmol, 2.0 eq.) and acetic acid (14 µL, 0.24 mmol, 2.0 eq.) in toluene (3.5 mL) was stirred at rt for 18 h. The reaction mixture was quenched by addition of a 0.1 M HCl solution. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was subjected to flash column chromatography (pentane/Et_2O 2:1) to afford the octalone **32** (42 mg, 82 µmol, 68 %) as a colorless solid.

M.p. = 132.3 – 134.5°C. TLC: R_f = 0.41 (SiO_2, pentane/Et_2O 2:1). $[\alpha]_D^{25}$ = +31.7° (c = 0.31, $CHCl_3$). FTIR (neat): $\tilde{\nu}$ = 2946, 2925, 1751, 1681, 1469, 1228, 1147, 980 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 6.37 (dd, *J* = 2.1, 0.9 Hz, 1H), 5.40 (t, *J* = 3.3 Hz, 1H), 4.63 (dd, *J* = 9.6, 2.0 Hz, 1H), 3.75 (dd, *J* = 9.6, 3.7 Hz, 1H), 2.48 (ddd, *J* = 17.0, 14.6, 5.0 Hz, 1H), 2.35 (dddd, *J* = 17.0, 4.4, 3.1, 1.0 Hz, 1H), 2.11 (s, 3H), 2.06 (ddd, *J* = 13.4, 5.1, 3.1 Hz, 1H), 1.78 – 1.62 (m, 2H), 1.29 (s, 3H), 1.11 – 0.96 (m, 31H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 199.4, 170.3, 166.9, 123.0, 77.3, 75.2, 72.3, 42.8, 38.7, 37.0, 33.4, 21.2, 19.1, 17.6 – 17.2 (8C), 13.0, 12.9, 12.4, 12.0, 11.0. HRMS (ESI) Exact mass calculated for $C_{26}H_{47}O_6Si_2^+$ $[M+H]^+$: 511.29057, found: 511.29098 and for $C_{26}H_{46}O_6Si_2Na^+$ $[M+Na]^+$: 533.27251, found: 533.27276.

(5a*R*,6*R*,7*R*,7a*R*,9*S*,11b*R*)-9-(2-hydroxypropan-2-yl)-2,2,4,4-tetraisopropyl-7,7a-dimethyl-10-oxo-5a,6,7,7a,8,9,10,11b-octahydronaphtho[1,2-*f*][1,3,5,2,4]trioxadisilepin-6-yl acetate (33): To a solution of octalone **32** (5.5 mg, 10.8 µmol, 1.0 eq.) in THF (0.3 mL) at –78°C was added a solution of LHMDS (1M in THF, 54 µL, 54 µmol, 5.0 eq.). After 1 h a solution of $ZnCl_2$ (1M in THF, 22 µL, 22 µmol, 2.0 eq.) was added and the reaction mixture was allowed to warm up to –40°C and stirred for 15 min at this temperature. Freshly distilled acetone (8 µL, 0.11 mmol, 10 eq.) was added and after stirring for 25 min, the reaction mixture was quenched by addition of an aq. tartaric acid solution (5 %). The mixture was extracted with Et_2O (3 x) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was subjected to flash column chromatography (pentane/Et_2O 2:1) to give the tertiary alcohol **33** (4.1 mg, 7.2 µmol, 67 %) as a colorless oil.

TLC: R_f = 0.41 (SiO_2, pentane/Et_2O 3:1). $[\alpha]_D^{22}$ = +40.5° (c = 0.21, $CHCl_3$). FTIR (neat): $\tilde{\nu}$ = 2945, 2868, 1751, 1653, 1464, 1377, 1226, 1125, 887 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 6.33 (d, *J* = 2.0 Hz, 1H), 5.41 (t, *J* = 3.3 Hz, 1H), 4.97 (brs, 1H), 4.62 (dd, *J* = 9.7, 2.0 Hz, 1H), 3.77 – 3.66 (m, 1H), 2.55 (dd, *J* = 14.6, 4.3 Hz, 1H), 2.12 (s, 3H), 2.03 (dd, *J* = 12.9, 4.4 Hz, 1H), 1.66 (dq, *J* = 7.1, 4.1 Hz, 1H), 1.48 (t, J = 13.8, 1H), 1.32 (s, 3H), 1.22 (s, 3H), 1.21 (s, 3H), 1.11 – 0.96 (m, 31H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 203.2, 170.2, 167.6, 123.6, 77.0, 75.1, 72.5, 72.2, 50.7, 43.1, 40.0, 39.4, 28.4, 24.9, 21.2, 19.0, 17.6 – 17.2 (8C), 13.0, 12.9, 12.4, 12.0, 11.0. HRMS (ESI) Exact mass calculated for $C_{29}H_{53}O_7Si_2^+$ $[M+H]^+$: 569.33243, found: 569.33286. Exact mass calculated for $C_{29}H_{52}O_7Si_2Na^+$ $[M+Na]^+$: 591.31428, found: 591.31437.

(5a*R*,6*R*,7*R*,7a*R*,9*S*,11b*R*)-2,2,4,4-tetraisopropyl-7,7a-dimethyl-10-oxo-9-(prop-1-en-2-yl)-5a,6,7,7a,8,9,10,11b-octahydronaphtho[1,2-*f*][1,3,5,2,4]trioxadisilepin-6-yl acetate (34): Tertiary alcohol **33** (18.7 mg, 33 µmol, 1.0 eq.) was dissolved in toluene (0.7 mL) and Burgess reagent (49 mg, 0.20 mmol, 6.1 eq.) was added. The reaction mixture was stirred at rt for 26 h, before it was diluted with H_2O and extracted with Et_2O (3 x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was subjected to flash column chromatography (pentane/Et_2O 7:1) to afford the isopropenylated compound **34** (9.7 mg, 17.6 µmol, 54 %) as a colorless solid.

M.p. = 108.5 – 112.2°C. TLC: R_f = 0.76 (SiO_2, pentane/Et_2O 3:1). $[\alpha]_D^{25}$ = +86.2° (c = 0.49, $CHCl_3$). FTIR (neat): $\tilde{\nu}$ = 2945, 2868, 1751, 1679, 1464, 1229, 1150, 980, 887 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 6.36 (d, *J* = 2.0 Hz, 1H), 5.41 (t, *J* = 3.3 Hz, 1H), 4.99 (t, *J* = 1.6 Hz, 1H), 4.82 (d, *J* = 1.7 Hz, 1H), 4.63 (dd, *J* = 9.6, 2.0 Hz, 1H), 3.76 (dd, *J* = 9.6, 3.8 Hz, 1H), 3.17 (dd, *J* = 14.4, 4.5 Hz, 1H), 2.12 (s, 3H), 2.00 (dd, *J* = 13.0, 4.6 Hz, 1H), 1.86 (t, *J* = 13.7 Hz, 1H), 1.74 (s, 3H), 1.69 (qd, *J* = 7.0, 3.0 Hz, 1H), 1.35 (s, 3H), 1.12 – 0.95 (m, 31H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 198.7, 170.2, 165.8, 143.4, 123.1, 114.5, 77.1, 75.3, 72.2, 50.2, 43.2, 42.9, 39.3, 21.2, 20.3, 19.1, 17.6 – 17.2 (8C), 13.0, 12.9, 12.3, 12.0, 11.0. HRMS (ESI) Exact mass calculated for $C_{29}H_{51}O_6Si_2^+$ $[M+H]^+$: 551.32187, found: 551.32224.

Guignarderemophilane C (1): The fully protected triol **34** (10 mg, 18 µmol, 1.0 eq.) was dissolved in THF (0.35 mL) and cooled to 0°C. A solution of TBAF (1 M in THF, 73 µL, 73 µmol, 4.0 eq.) was added and the reaction mixture was stirred at 0°C for 50 min, before it was treated with sat. aq. NH_4Cl solution. The layers were separated and the aqueous layer was extracted with EtOAc (3 x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude material was dissolved in a solution of NH_3 (7 M in MeOH, 0.35 mL) and stirred at rt for 2 h. The solvent was evaporated (at 30°C bath temperature) and the residue was purified by flash column chromatography (CH_2Cl_2/MeOH 12:1) to afford a 4.6:1 mixture of guignarderemophilane C (**1**) and D (**2**) (3.5 mg, 13.1 µmol, 72 % over two steps). For analytical purposes, the mixture of **1** and **2** was purified by semi-preparative HPLC using the conditions given below. The residue was dissolved in a mixture of H_2O/MeCN/MeOH (10:4:1, 0.8 mL) and in total eight runs had to be carried out with injection of 100 µL of the sample per run. Two fractions were collected from 18.00 to 19.20 min (fraction 1), and from 19.20 to 21.00 min (fraction 2), respectively. The first fraction gave pure guignarderemophilane C (**1**) (2.2 mg, 63 %) and the second fraction gave a 1:1 mixture of guignarderemophilanes C (**1**) and D (**2**) (1.1 mg, 31 %) after concentration by rotary evaporator and lyophilizer.

Column: Synergi Hydro-RP 10 µm 80 Å, 150 mm x 10.0 mm; solvent A: H_2O; solvent B: MeCN; flow = 4.6 mL/min; T = rt; UV detection at 222 nm; solvent system: isocratic, [B] = 18 %.

TLC: R_f = 0.43 (SiO_2, CH_2Cl_2/MeOH 12:1) $[\alpha]_D^{27}$ = +35.0° (c = 0.88, MeOH). FTIR (neat): $\tilde{\nu}$ = 3401, 2968, 2940, 2881, 1662, 1443, 1327, 1132, 1101, 1079, 889 cm^{-1}. ^1H NMR (500 MHz, MeOD) δ = 6.20 (d, *J* = 2.0 Hz, 1H), 4.93 (t, *J* = 1.7 Hz, 1H), 4.82 – 4.80 (m, 1H), 4.48 (dd, *J* = 10.4, 2.0 Hz, 1H), 3.86 (t, *J* = 3.0 Hz, 1H), 3.38 (dd, *J* = 10.4, 3.3 Hz, 1H), 3.24 (dd, *J* = 14.4, 4.6 Hz, 1H), 1.99 (dd, *J* = 13.0, 4.6 Hz, 1H), 1.88 (t, *J* = 13.7 Hz, 1H), 1.70 (t, *J* = 1.0 Hz, 3H), 1.51 (qd, *J* = 7.1, 2.8 Hz, 1H), 1.41 (s, 3H), 1.14 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, MeOD) δ = 201.7, 172.6, 144.9, 122.0, 114.7, 77.4, 75.6, 70.1, 51.3, 45.9, 44.4, 40.8, 20.2, 19.8, 11.8. HRMS (ESI) Exact mass calculated for $C_{15}H_{22}O_4Na^+$ $[M+Na]^+$: 289.14103, found: 289.14085.

Guignarderemophilane D (2): A solution of guignarderemophilane C (**1**) (2.0 mg, 7.5 µmol, 70 %) in NaOMe (0.5 M in MeOH, 1.0 mL) was stirred for 6 h at 0°C. The reaction was quenched by addition of sat. aq. NH_4Cl solution and the resulting turbid mixture was extracted with EtOAc (3 x). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude residue was subjected to flash column chromatography (CH_2Cl_2/MeOH 14:1) to give guignard-eremophilane D (**2**) (1.4 mg, 5.3 µmol, 70 %) as a colorless solid.

TLC: R_f = 0.23 (SiO_2, CH_2Cl_2/MeOH 14:1) $[\alpha]_D^{25}$ = +38.2° (c = 0.70, MeOH). FTIR (neat): $\tilde{\nu}$ = 3401, 2965, 2882, 1652, 1626, 1370, 1297, 1072, 1017 cm^{-1}. ^1H NMR (500 MHz, MeOD) δ = 6.20 (d, *J* = 2.2 Hz, 1H), 4.44 (dd, *J* = 10.4, 2.2 Hz, 1H), 3.86 (t, *J* = 2.9 Hz, 1H), 3.39 (dd, *J* = 10.3, 3.2 Hz, 1H), 2.98 (d, *J* = 13.6 Hz, 1H), 2.12 (d, *J* = 14.3 Hz, 1H), 2.08 (d, *J* = 2.1 Hz, 3H), 1.89 (d, *J* = 1.4 Hz, 3H), 1.56 (qd, *J* = 7.1, 2.7 Hz, 1H), 1.18 (d, J = 1.4 Hz, 3H), 1.17 (s, 3H). ^{13}C NMR (126 MHz, MeOD) δ = (126 MHz, MeOD) δ = 194.2, 171.3, 145.6, 128.6, 124.2, 77.5, 75.6, 70.1, 44.7, 43.6, 43.1, 22.8, 22.4, 20.1, 12.1. HRMS (ESI) Exact mass calculated for $C_{15}H_{23}O_4^+$ $[M+H]^+$: 267.15909, found: 267.15899 and $C_{15}H_{22}O_4Na^+$ $[M+Na]^+$: 289.14075, found: 289.14084.

Supplementary Material

Additional experimental information, ^1H and ^{13}C NMR spectra, HPLC chromatograms and CD spectra are given in the Supporting information for this article, available on the WWW under http://dx.doi.org/10.1002/MS-number.

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Author Contribution Statement

A. I., R. L. and *K. G.* designed the project and prepared the manuscript. *A. I.* and *R. L.* performed the experiments, and *A. I., R. L.* and *K. G* analyzed the data.

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